(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 520 406 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **92110636.5**

(22) Date of filing: **24.06.92**

(51) Int. Cl.5: **C07D 215/14**, C07D 405/06, A61K 31/47

(30) Priority: **24.06.91 JP 151810/91**
20.05.92 JP 127277/92

(43) Date of publication of application:
30.12.92 Bulletin 92/53

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE

(71) Applicant: **NISSAN CHEMICAL INDUSTRIES LTD.**
7-1, 3-chome Kanda-Nishiki-cho
Chiyoda-ku Tokyo(JP)

(72) Inventor: **Ohara, Yoshio, c/o Nissan Chem. Ind., Ltd.**
Chuo Kenkyusho, 722-1, Tsuboi-cho
Funabashi-shi, Chiba-ken(JP)
Inventor: **Suzuki, Mikio, c/o Nissan Chem. Ind., Ltd.**
Chuo Kenkyusho, 722-1, Tsuboi-cho
Funabashi-shi, Chiba-ken(JP)
Inventor: **Yanagawa, Yoshinobu, c/o Nissan Chem. Ind., Ltd.**
Chuo Kenkyusho, 722-1, Tsuboi-cho
Funabashi-shi, Chiba-ken(JP)
Inventor: **Iwasaki, Hiroshi, c/o Nissan Chem. Ind., Ltd.**
Chuo Kenkyusho, 722-1, Tsuboi-cho
Funabashi-shi, Chiba-ken(JP)
Inventor: **Miyachi, Nobuhide, c/o Nissan Chem. Ind., Ltd.**
Chuo Kenkyusho, 722-1, Tsuboi-cho
Funabashi-shi, Chiba-ken(JP)

(74) Representative: **Wächtershäuser, Günter, Dr.**
Tal 29
W-8000 München 2(DE)

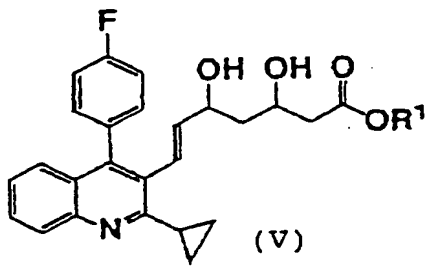
(54) Diastereomer salt of optically active quinolinemevalonic acid.

(57) A diastereomer salt of optically active quinolinemevalonic acid of the formula ((-)I•(+)II):

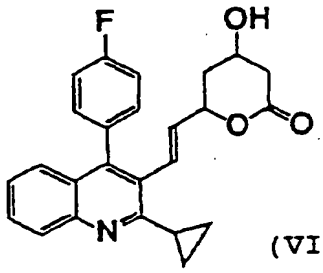
EP 0 520 406 A1

The present invention relates to an important intermediate for the preparation of optically active quinolinemevalonic acid derivatives useful for the prevention or treatment of hyperlipemia, arteriosclerosis, etc. and a method for optically resolution thereof.

A quinolinemevalonic acid compound of the formula (V) and a quinolinemevalonolactone compound of the formula (VI):



(V)

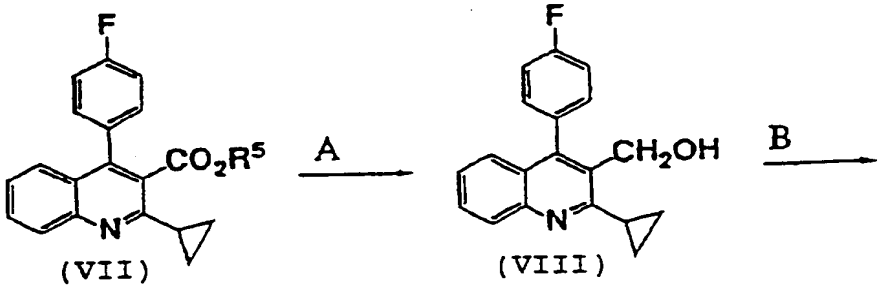


(VI)

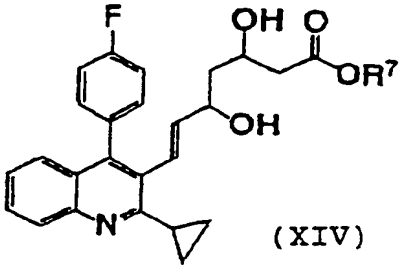
wherein R^1 is a hydrogen atom, a C_{1-4} lower alkyl group such as a methyl group, an ethyl group, a n-propyl group, an i-propyl group, a t-butyl group, a n-butyl group, an i-butyl group, a s-butyl group, or Na, K, 1/2Ca or $HNR^2R^3R^4$ wherein each of R^2, R^3 and R^4 is hydrogen, a C_{1-3} lower alkyl group or a 2-hydroxyethyl group, or when R^2 is hydrogen or methyl, R^3 and R^4 together form $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$ or $-(CH_2)_2-NH-(CH_2)_2-$, are racemic mixtures or compounds having four optical isomers, as disclosed in Japanese and European Unexamined Patent Publication Nos. 279866/1989 and 304063, and they are strong inhibitors against HMG-CoA reductase which is a rate limiting enzyme for the biosynthesis of cholesterol and thus expected to be useful as drugs for the prevention and treatment of hyperlipemia, arteriosclerosis, etc.

Further, quinolinecarboxylic acid derivatives as HMG-CoA reductase inhibitors are disclosed, for example, in the following literatures: German Patent DE-3905908, U.S. Patent 4,761,419, U.S. Patent 4,923,861 and European Patent Publication EP 356788A.

As disclosed in Japanese and European Unexamined Patent Publication Nos. 279866/1989 and 304063, the compounds of the formulas (V) and (VI) can be prepared as follows:

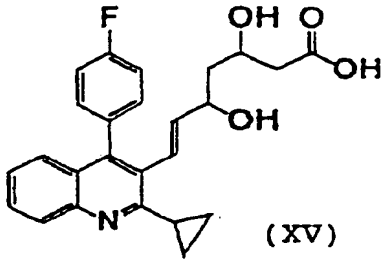


(VII) (VIII)



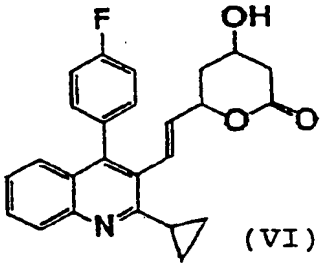
(XIV)

H



(XV)

J



(VI)

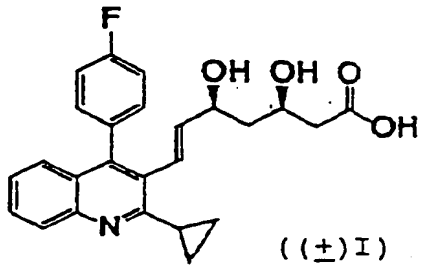
In the above formulas, each of R^5, R^6 and R^7 is a C_{1-4} lower alkyl group such as a methyl group, an ethyl group, a n-propyl group, an i-propyl group, a t-butyl group, a n-butyl group, an i-butyl group or a s-butyl group.

Step A is a reduction reaction of an ester (VII) to a primary alcohol (VIII), and the reaction can be conducted in a solvent such as tetrahydrofuran or toluene at a temperature of from -20 °C to 20 °C, preferably from -10 °C to 10 °C, using various metal hydrides, preferably diisobutylaluminum hydride.

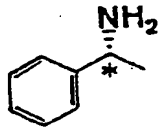
Step B is an oxidation reaction of the primary alcohol (VIII) to an aldehyde (IX), and the reaction can be conducted using various oxidizing agents. Preferred is a method wherein oxidation is conducted at a temperature of from 0 °C to 25 °C using pyridinium chlorochromate in methylene chloride, a method wherein oxidation is conducted using oxalyl chloride, dimethyl sulfoxide and a tertiary amine (such as triethylamine) (Swern oxidation), a method wherein oxidation is conducted using phosphorus pentoxide, dimethyl sulfoxide and a tertiary amine (such as triethylamine) or a method wherein oxidation is conducted using sulfur trioxide-pyridine complex.

Step C is a reaction for the preparation of an α,β-unsaturated carboxylic acid ester (X), whereby a transform α,β-unsaturated carboxylic acid ester (X) can be obtained by so-called Horner-Wittig reaction using an alkoxycarbonylmethyl phosphonate. As the base, sodium hydride, potassium-t-butoxide or the like is employed, and the reaction is conducted in dry tetrahydrofuran at a temperature of from -30 °C to 0 °C, preferably from -20 °C to -15 °C.

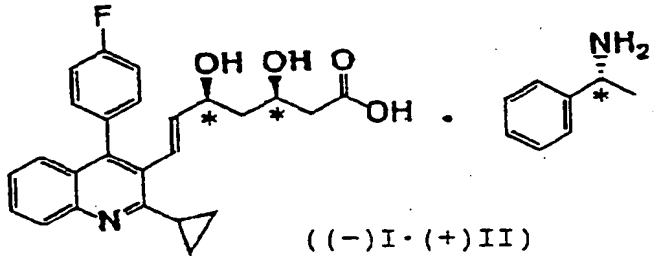
The present invention provides also a method for optical resolution of quinolinemevalonic acid ((±)I), which comprises reacting the quinolinemevalonic acid of the formula ((±)I) with D(+) phenethylamine of the formula ((+)II), and separating the resulting diastereomer salt of optically active quinolinemevalonic acid of the formula ((-)I•(+)II):



((±)I)

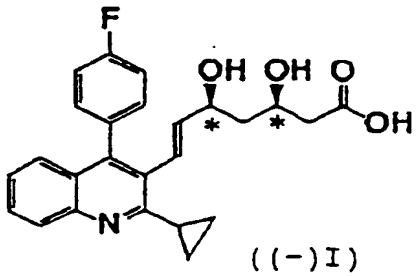


((+)II)



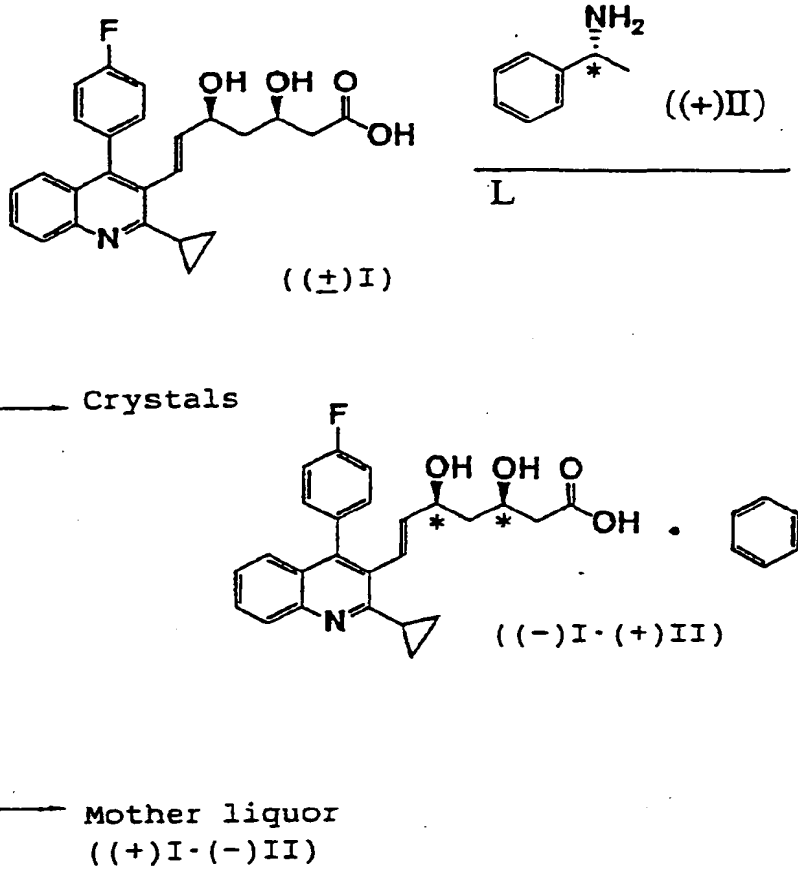
((−)I•(+)II)

Further, the present invention provides a process for producing optically active quinolinemevalonic acid of the formula ((-)I), which comprises treating the diastereomer salt of optically active quinolinemevalonic acid of the formula ((-)I•(+)II), with an acid:



((−)I)

Still further, the present invention provides a process for producing optically active quinolinemevalonolactone of the formula (III), which comprises dehydrating the optically active quinolinemevalonic acid of the formula ((-)I):


F
OH OH O
OH
N
((±)I)
NH2
((+)II)
L
Crystals
((−)I·(+)II)
Mother liquor
((+)I·(−)II)

Step O is a step of reacting the optically active quinolinemevalonic acid ((-)I) with a base to obtain an optically active quinolinemevalonic acid salt (IV). The base used here may be piperazine, morpholine, diethanolamine, triethanolamine, NaOH, KOH, $Ca(OH)_2$ or CaO.

In step P, the optically active quinolinemevalonic acid salt (IV) can be obtained from the diastereomer salt of optically active quinolinemevalonic acid ((-)I•(+)II) without isolating the optically active quinolinemevalonic acid ((-)I). Namely, by adding an aqueous solution of alkali metal hydroxide (such as sodium hydroxide or potassium hydroxide) to the diastereomer salt of optically active quinolinemevalonic acid ((-)I•(+)II), it is possible to directly obtain an alkali metal salt (such as a quinolinemevalonic acid salt (IV) wherein R^8 is Na or K). Further, by adding an aqueous solution of an alkaline earth metal chloride (such as $CaCl_2$) to such an aqueous alkali metal salt solution, it is possible to obtain an alkaline earth metal salt (such as a quinolinemevalonic acid salt (IV) wherein R^8 is 1/2Ca).

Now, the present invention will be described in detail with reference to Examples, but it should be understood that the present invention is by no means restricted by such specific Examples.

REFERENCE EXAMPLE 1

(±)-(E)-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-cyclopropylquinolin-3'-yl]hept-6-ene acid compound ((±)I)

60 g of (±)-(E)-ethyl-3,5-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-cyclopropylquinolin-3'-yl]hept-6-enoate (a compound (XVI) wherein R^9 is Et) was suspended in 100 mℓ of ethanol, and 200 mℓ of a 1N sodium hydroxide aqueous solution was added thereto. As the reaction proceeded, the suspension became a uniform solution. After completion of the hydrolysis, 200 mℓ of 1N hydrochloric acid was added thereto. This reaction solution was extracted with 500 mℓ of dichloromethane to obtain the desired compound ((±)I).

H-NMR($CDCl_3$), δppm

1.0-1.1 (m, 2H), 1.3-1.4 (m, 3H), 1.5-1.6 (m, 1H), 2.3-2.4 (m, 1H), 2.51 (d, 2H, J = 6.1), 2.8-3.5 (b, 3H), 4.1-4.2 (m, 1H), 4.4-4.5 (m, 1H), 5.59 (dd, 1H, J = 6.1, J = 16.1), 6.63 (d, 1H, J = 6.1), 7.1-7.4 (m, 6H), 7.5-7.7 (m, 1H), 7.9-8.0 (m, 1H).

REFERENCE EXAMPLE 2

Resolution of a diastereomer salt using a chiral organic amine

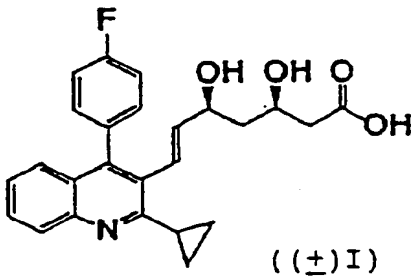
To the dichloromethane solution of the compound ((±)I) obtained in Reference Example 1, 1 equivalent of a chiral organic amine as identified in Table 1 was added, and then the solvent was distilled off to obtain a residue containing the corresponding diastereomer salt. Except for the case where the residue was oil, the residue was dissolved under heating in ten times by weight of methyl isobutyl ketone-dimethylformamide (20:1, v/v), followed by cooling to a temperature of from 10 to 25°C for crystallization. For the optical yield, the obtained diastereomer salt was treated with an acid and then converted to lactone, and the optical yield was measured by a high performance liquid chromatography using an optical resolution column (chiraSpher, tradename, manufactured by E. Merck Company).

Resolution agent (chiral organic amine)	Chemical yield (%)	Optical yield (%ee)
D(+)phenethylamine	44	73
R(+)α-(p-tolyl)ethylamine	30[1)]	60
R(-)2-amino-1-butanol	80	0
D(-)α-phenylglycinol	-[2)]	-
(-)N-benzyl-α-phenylethylamine	-[2)]	-
(-)p-bromo-α-phenylethylamine	-[2)]	-

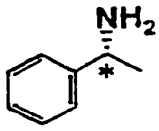
1) A gel substance precipitated.
2) The diastereomer salt was an oily substance.

EXAMPLE 1

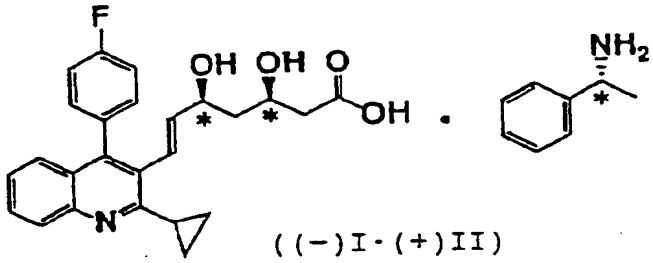
(E)-3(R)-5(S)-dihydroxy-7-[4'-(4''-fluorophenyl)-2'-cyclopropylquinolin-3'-yl]hept-6-ene acid•D(+)phenethylamine salt compound ((-)I•(+)II)



((±)I)

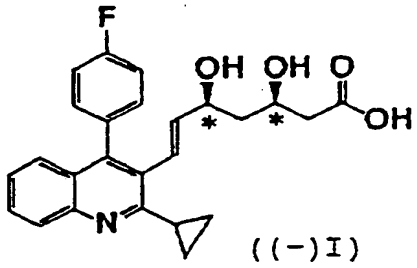


((+)II)



((−)I·(+)II)

3. A process for producing optically active quinolinemevalonic acid of the formula ((-)I), which comprises treating the diastereomer salt of optically active quinolinemevalonic acid of the formula ((-)I•(+)II) as defined in Claim 1, with an acid:



((−)I)

4. A process for producing optically active quinolinemevalonolactone of the formula (III), which comprises dehydrating the optically active quinolinemevalonic acid of the formula ((-)I) as defined in Claim 3:

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 11 0636

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y	EP-A-0 409 281 (WARNER-LAMBERT COMPANY) * page 4-5 *	1-6	C07D215/14 C07D405/06 A61K31/47
Y	DE-A-3 905 908 (BAYER AG) * page 13, line 50-55 *	1-6	
Y	EP-A-0 430 129 (TANABE SEIYAKU CO., LTD.) * page 4, line 38-45 *	1-6	
Y	EP-A-0 411 420 (BAYER AG) * page 13, line 13-18 *	1-6	
Y	US-A-4 567 289 (MERCK & CO. INC.) * column 13, line 17-22; column 27-29, example 13,14 *	1-6	
D,A	EP-A-0 304 063 (NISSAN CHEMICAL INDUSTRIES LTD.) * claims *	1	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)
C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	14 SEPTEMBER 1992	VAN BIJLEN H.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)